Alcohol Consumption and Breast Cancer [1]

Elizabeth B. Harvey, *Ph.D.*, [2,3,4] **Catherine Schairer**, *M.S.*, [2] **Louise A. Brinton**, *Ph.D.*, [2] **Robert N. Hoover**, *M.D.*, [2] *and* **Joseph F. Fraumeni, Jr.**, *M.D.* [2]

ABSTRACT—The association between alcohol consumption and breast cancer was investigated in a case-control study involving 1,524 cases and 1,896 controls identified through a nationwide screening program. Ever drinking alcohol was not associated with any substantial increase in risk [odds ratio (OR)=1.1; 95% confidence interval (CI)=1.0-1.3], but there was a significant trend in risk with increasing average weekly intake ($P<.04$). Women who had one or fewer drinks daily (83% of all drinkers) did not experience any excess risk compared to nondrinkers, but significant excess risks were observed among those who drank from 1 to 2 (OR=1.3; 95% CI=1.0-1.7) or more than 2 (OR=1.7; 95% CI=1.2-2.4) drinks a day. An increased risk associated with alcohol consumption was evident only for those who drank at younger ages (<30 yr), regardless of current consumption. Alcohol effects were adjusted for a variety of factors, including reproductive history, socioeconomic indicators, and obesity, but none exerted any appreciable confounding influence. The results support an association between moderate alcohol consumption in early life and subsequent breast cancer risk, although interpretation should be cautious in the absence of dietary information.—JNCI 1987; 78:657-661.

Several epidemiologic studies have implicated modest alcohol consumption with an increased risk of developing breast cancer (*1-6*). Reported ORs have been in the range of 1.5-2 for women who have consumed levels of alcohol ranging from 2 to 3 or more drinks per day versus those who do not drink.

The strongest support of an association has been found in hospital-based case-control studies utilizing controls with other cancers (*1, 2, 5*) or nonmalignant diseases (*1, 3, 4*). One prospective study, which eliminated the potential bias of hospital controls, also yielded a positive finding (*6*). In addition, follow-up studies of alcoholics have indicated an increased risk of breast cancer mortality (*7-10*).

Other studies, however, utilizing hospital cases and controls (*11-13*) as well as community controls (*14-16*), have failed to find positive associations. Correlational studies of alcohol consumption and breast cancer mortality have also provided inconsistent results (*17-20*). Furthermore, experimental data are scant (*21*) and biological mechanisms are unclear (*22-24*).

To evaluate further the association of alcohol use and breast cancer, we analyzed data from a multicenter breast cancer screening program in which extensive information was collected on standard breast cancer risk factors as well as on alcohol consumption.

SUBJECTS AND METHODS

The study population consisted of participants in the Breast Cancer Detection Demonstration Project, a breast cancer screening program involving over 280,000 women at 29 centers. Sponsored by the American Cancer Society and the National Cancer Institute, this program enrolled women from 1973 to 1975 for a 5-year period during which time annual breast examinations, mammography, and thermography were performed. Previous publications have discussed the methodology of the initial case-control study conducted among women whose breast cancer was detected during the first several years of the screening program (*25, 26*). In an extension of the study, the questionnaire was expanded to include questions on alcohol consumption. The present investigation concentrates on women whose breast cancer was detected during the latter years of the screening program, specifically between June 1977 and November 1980. Controls were selected from women who had not been recommended for or did not undergo a biopsy during screening. Controls were stratified to cases on center, race (white, black, oriental, other), age (same 5-yr age groups), time of entry (same 6-mo period), and length of participation in the program.

Home interviews were conducted for 1,799 cases (74.4%) and 2,208 controls (89.9%) on the average of 5 years after breast cancer diagnosis. The major reasons for nonresponse were death of the study subject (17.3% of the cases vs. 2.3% of the controls) and refusal (5.4 vs. 5.7%). The remaining subjects either could not be located or were unable to participate due to illness. Women who reported a history of breast cancer prior to entry into the screening program (73 cases and 28 controls) were excluded from the analysis, as were those for whom alcohol information was not available (23 cases and 34 controls). The analysis was further limited to white subjects, who comprised 94% of the entire population. Thus the final study group consisted of 1,524 cases and 1,896 controls.

Information on alcohol consumption was collected by asking a woman if she had ever consumed beer, wine, or liquor, and if so, the number of servings per week during three age periods throughout her life up until entry

ABBREVIATIONS USED: CI = confidence interval; OR = odds ratio.

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[2] Epidemiology and Biostatistics Program, Division of Cancer Etiology, National Cancer Institute, National Institutes of Health, Public Health Service, U.S. Department of Health and Human Services.

[3] *Present address:* CENTOCOR, 244 Great Valley Parkway, Malvern, PA 19355.

[4] *Address reprint requests to* Dr. Harvey at the Landow Building, Room 3A22, National Institutes of Health, Bethesda, MD 20892.

into the screening program: less than 30 years of age, 30-49 years, or 50 years and older. Measures of the alcohol content (grams of ethanol per ounce) of specified servings of beer, wine, and liquor are listed in table 1 (*27*). For purposes of analysis, a weekly estimate was calculated by multiplying the grams of ethanol in each beverage by the total number of servings per week and then by summing the total intake of the three beverage categories over each age period. An overall weighted average was calculated taking into account the years spent in each age category; 21 years was chosen as an arbitrary lower limit for the under-30 age group. Women who did not provide information on number of servings but who indicated that they were "infrequent" drinkers were assigned a value of .25 drinks a week.

The effect of alcohol consumption on breast cancer risk was measured by the OR (*28*). Adjustment for the influence of individual confounding variables was done by stratified analyses; maximum likelihood estimates of combined ORs and 95% CIs were derived (*29*). Statistical significance of dose-related trends in ORs was assessed by an extension of the Mantel-Haenszel test procedure with the use of the one-tailed *P*-values (*30*). Assessment of confounding of more than one variable at a time was achieved with logistic analyses (*31*). Logistic regression was used also to test for interaction and the effects of individual beverages, i.e., beer, wine, and liquor (*32*). Matched analyses were performed (*33*), but, due to the similarity in the results of the analyses, only the unmatched estimates are presented.

RESULTS

Seventy-seven percent of the cases and 75% of the controls reported ever having consumed alcohol. The mean weekly average alcohol intake was 56 g; consumption was higher for those entering the screening program at 30-49 years as opposed to those entering at older ages (67 g vs. 49 g).

Table 2 shows the ORs of breast cancer according to various measures of alcohol consumption. There was no substantial risk associated with drinking compared to risk associated with nondrinking (OR=1.1; 95% CI=1.0-1.3). A significant trend in risk ($P<.04$), however, was observed with increasing alcohol consumption. Women who had one drink or less daily did not experience any excess risk compared to that of nondrinkers, but those consuming 92-183 g of alcohol per week (1-2 drinks/day) or over 183 g of alcohol (>2 drinks/day) had significantly increased risks of developing breast cancer compared to risks of women who never imbibed (OR=1.3 and OR=1.7, respectively). When the highest lifetime average group was divided into several categories, the ORs associated with drinking 2.5, 3, and more than 4 drinks daily were 1.9, 2.0, and 1.7, respectively.

Although slight differences were found between drinkers and nondrinkers with respect to income, education, smoking status, age at the birth of their first child, and weight, adjustment for these factors did not appreciably confound any of the observed associations. In addition, risks associated with alcohol consumption were not affected by adjustment for age at menarche, menopausal status, age at menopause, oral contraceptive use, menopausal hormone use, previous breast disease, or family history of breast cancer in a mother or sister. Therefore, unadjusted estimates are presented.

The effect of age at alcohol consumption was assessed by examining the risks of all drinkers who entered the screening program before and after age 50 by current and past drinking habits (table 3). Since there was no risk associated with less than 14 g of alcohol per week in each age period, the referent category included women

TABLE 1.—*Amount of pure ethanol (g) per serving by type of alcoholic beverage*

Type of beverage	Ethanol per oz, g	Serving size, oz	Ethanol per serving, g
Beer	1.1	12	13.2
Wine	2.9	4	11.6
Hard liquor	9.4	1.5	14.1

TABLE 2.—*ORs of breast cancer according to average weekly alcohol consumption*

Category	Cases	Controls	OR	95% CI
Nondrinkers	346	477	1.00	
Ever drank	1,178	1,419	1.14	1.0-1.3
Weekly average,[a] g (drinks/wk or day)				
.1-13 (1/wk)	533	657	1.12	0.9-1.3
14-91 (1/wk-1/day)	414	537	1.06	0.9-1.3
92-182 (1-2/day)	148	156	1.31	1.0-1.7
≥183 (2/day)	83	69	1.66	1.2-2.4

Chi for linear trend=1.82, $P=.04$

[a] 13 g is the approximate equivalent of 1 drink. Unknown values are excluded from this analysis.

TABLE 3.—*ORs of breast cancer in women entering the screening program prior to and after the age of 50 by age of alcohol consumption*[a]

Consumption age, yr	Alcohol consumed per week, g			
	<14	14-91	92-182	≥183
Women entering prior to age 50				
<30	1.0 (267)	0.95 (120)	1.77 (38)	1.68 (21)
30-49	1.0 (196)	0.92 (140)	0.91 (66)	0.78 (44)
Women entering at age >50				
<30	1.0 (496)	1.15 (155)	1.53[b] (54)	1.95 (26)
30-49	1.0 (398)	0.91 (196)	0.96 (83)	1.45 (55)
≥50	1.0 (383)	0.92 (186)	0.90 (94)	0.90 (69)

[a] Numbers of exposed cases are shown *in parentheses*. Referent groups are women who drank <14 g or nondrinkers in specified age category only. All women who never consumed alcohol are excluded.
[b] $P<.05$.

TABLE 4.—*ORs of breast cancer for recent[a] alcohol consumption versus alcohol consumption under age 30*

Consumption under age 30, g	Recent consumption, g[b]			
	0-13	14-91	92-182	≥183
0-13 (1/wk)	1.14 (520)	1.04 (162)	0.81 (49)	1.30 (33)
14-91 (1/wk-1/day)	1.29 (44)	1.00 (141)	1.32 (65)	0.84 (25)
92-182 (1-2/day)	1.06 (10)	1.80 (17)	1.72[c] (40)	2.15[c] (25)
≥183	2.30 (5)	—[d] (6)	1.65 (6)	1.72[c] (30)

[a] Consumption during time period in which subject entered screening program.
[b] Numbers of exposed cases are shown *in parentheses*. Unknowns are excluded from analysis. Referent group included women who never drank.
[c] $P<.05$.
[d] There were 0 controls in this cell.

with low alcohol consumption in a specific age group as well as those who never imbibed in that age group. The effect of drinking at an early age was evident. Consumption of 1-2 or more than 2 drinks a day when less than age 30 was associated with increased risks of breast cancer (OR=1.8 and 1.7 for women <50 at entry into the screening program and OR=1.5 and 2.0 for women 50 or older). Women entering the screening program at 50 years or older who were in the highest drinking category when 30-49 years old also experienced an increased risk (OR=1.4). Recent alcohol consumption, i.e., drinking during the age period corresponding to age at entry into the screening program, was not associated with any elevated risks in either age group. These patterns according to age at consumption were also evident when the risks were adjusted for one another, as well as when they were evaluated separately, as in table 3.

To define further the influence of drinking at a young age, we performed a cross-tabulation of risks for recent consumption versus those associated with drinking prior to 30 years of age (table 4). Although the case numbers are small in certain cells, an increased risk appeared to occur among women consuming more than 2 drinks a day while under age 30, regardless of recent consumption, whereas no appreciable increase in risk was related to recent consumption of an equivalent amount among women with low to moderate intake of alcohol before age 30.

To determine whether the apparent age susceptibility was due instead to a latent effect, we stratified age-specific consumption estimates by age at breast cancer diagnosis to derive crude estimates of latency. For consumption prior to age 30, the risks did not vary according to age at diagnosis, suggesting that a latent effect was not present. We did not, however, have sufficient information to evaluate equivalent latent periods for the other age categories.

The risks for consumption of alcohol prior to the age of 30 according to type of beverage consumed are shown in table 5. These estimates, each adjusted for the other two types of alcohol consumption, indicate that the elevated risks for women drinkers less than 30 years of age were influenced by liquor and beer and not by wine. We also tested for beverage differences using logistic models by successively adding beverage coefficients (linear and quadratic) in various combinations and then by calculating likelihood ratio statistics (*33*). Consistent with the results presented in table 5, wine did not produce any effects beyond that of beer or liquor alone, whereas both beer and liquor accounted for significantly more risk than that from one beverage alone. The lack of a wine effect, however, could be due to the small number of moderate wine drinkers.

Among women drinking prior to the age of 30, interactions of alcohol consumption levels were examined according to a number of breast cancer risk factors, e.g., menopausal status, family history, age at first birth, exogenous hormone use, and age at menarche. No significant effect modification was found.

DISCUSSION

Although this study found no significant excess breast cancer risk associated with ever drinking alcohol, a significant trend in risk was observed with increasing alcohol consumption. Women whose weekly average alcohol intake was equal to 1 or more alcoholic beverages per day had significantly elevated risks on the order of approximately 50%. The adverse effects of alcohol appeared related to drinking practices prior to 30 years of age, whereas current drinking did not affect risk. The increased risk associated with drinking at young ages was influenced by consumption of liquor and beer, but not wine.

Our overall findings are consistent with several earlier

TABLE 5.—*ORs[a] of breast cancer according to average weekly alcohol consumption under age 30 by type of beverage[b]*

Beverage	Alcohol consumption, g			
	0	.1-13	14-91	≥92
Liquor	1.0 (482)	0.99 (441)	1.00 (193)	2.05 (62)
Beer	1.0 (670)	1.10 (355)	1.11 (105)	1.71 (48)
Wine	1.0 (641)	1.08 (449)	1.01 (78)	0.77 (10)

[a] Adjusted for all other alcohol consumption.
[b] All risks are relative to those who did not drink the beverage in question in a specified category. All women who never consumed alcohol are excluded. Numbers of exposed cases are shown *in parentheses*. Unknown values are excluded from this analysis.

studies of breast cancer (*1–6*). Since other investigators have not evaluated timing of exposure, it is difficult to interpret effects associated with drinking at younger ages. This finding could be indicative of an age susceptibility or a latent effect. To the extent that we could examine the data, it appears to be the former, but we did not have sufficient information to make a complete evaluation. The relationship, however, is consistent with the array of breast cancer risk factors (i.e., age at menarche, age at first birth, family history, and ionizing radiation exposure) that seem to exert their influence at relatively young ages.

The types of alcoholic beverage related to risk in our study (liquor and beer) are not entirely consistent with those of previous studies; one report implicated beer and wine (*4*), whereas another reported risks associated with all three types (*5*). A third study found an association with liquor and wine, but no dose response was seen (*2*). It is difficult to reconcile these inconsistencies other than to infer that small numbers may have resulted in chance findings.

Although supported by other studies of breast cancer (*1–6*), the risk associated with alcohol in our study was of a low order of magnitude and associated with only moderate levels of drinking. Other case-control studies, however, have yielded negative results (*11–16*). Reasons for this discrepancy are unclear, but it has often been difficult to gather sufficient information on heavy drinkers. Only 5% of the women in our study reported 2 or more drinks per day. Even though over 75% of the subjects consumed alcohol in their lifetime, almost half of these women had an average intake of 1 drink or less a week and over 80% had 1 drink or less a day. Little is known about women who drink excessively, and it is difficult to evaluate their selective participation in epidemiologic studies. Cohort studies focusing on alcoholics have reported an increased risk of mortality from breast cancer (*7–10*) although generally based on small numbers.

It is interesting that most of the evidence linking breast cancer to alcohol use has come from hospital-based case-control studies. Two studies from France and Australia, however, have indicated that hospital-based controls tend to drink less than the general population (*4, 16*), which could have resulted in overestimates of risk. If this is also true in the United States, our study, which is not based on a hospital population, strengthens the evidence favoring a positive association. It should be kept in mind that the study did involve a self-selected population. The fact, however, that both cases and controls were self-selected should minimize this potential bias.

In evaluating our results, it is important to note that a large percentage of cases versus controls died before being interviewed. If survival were different for moderate drinkers versus nondrinkers, our results could be biased, either toward or away from the null.

Another limitation of our study is the lack of dietary information. It has been reported that obesity and high fat intake are associated with breast cancer (*34*), so that dietary factors correlated with alcohol use might confound the observed association. Although high-fat diets have promoted the incidence of mammary tumors in rats (*35*), the epidemiologic evidence in humans is based mainly on correlational rather than analytical studies, and a recent study from Italy found no indication that dietary factors, including fat and caloric intake, confounded the positive association of alcohol with breast cancer (*5*).

Although mechanisms by which alcohol might exert an adverse effect on breast tissue are unclear, several hypotheses have been proposed, including hepatic effects on estrogen or lipid metabolism or interference with the hepatic clearance function that might increase target organ exposure to mammary carcinogens or promoters (*22, 23, 36*). It has also been suggested that alcohol increases risk by stimulating the secretion of prolactin (*37, 38*), which is reported to enhance the growth of mammary tumors in rats (*39*). Alcohol also alters the physical-chemical characteristics of cell membranes (*40*), and experimental models of breast carcinogenesis have suggested that disruption of membrane function or cell-to-cell communication might be involved (*41*). In addition, nitrosamines have been detected in over 18 U.S. beers and in several brands of scotch (*42*). Although not implicated in human breast cancer, certain nitroso compounds have been linked to mammary tumors in laboratory animals (*43*). Phytoestrogens have also been identified in hops, and nonalcoholic bourbon contains three phytoestrogens that have been reported to bind to estrogen receptors present in breast cancer cells [(*44*) and Gavaler S, Rosenblum E, Van Thiel DH, et al.: Unpublished data].

In summary, our study provides additional epidemiologic evidence that moderate levels of alcohol consumption may increase the risk of breast cancer. Despite the consistency of the positive studies observed to date, a causal relationship has not been established. So that the issue can be resolved, further studies are needed that obtain more complete information on drinking habits, particularly at young ages, and on correlated risk factors, including those of a dietary nature.

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